

The blood pressure lowering potential of sulodexide – a systematic review and meta-analysis

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Sulodexide consists of glycosaminoglycans that are known to play an important role in endothelial function and sodium homeostasis.
- Previous studies have concentrated on the anti-albuminuric, but not BP lowering, potential of sulodexide.

WHAT THIS STUDY ADDS

- In comparison with control treatment, sulodexide results in a significant BP reduction.
- In patients with hypertension, the BP lowering potency of sulodexide may be similar to BP reductions achieved with single antihypertensive drugs.
- The systemic effects of sulodexide on BP, therefore, need to be considered in regard to anti-albuminuric efficacy.

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AIMS

Sulodexide is a highly purified mixture of glycosaminoglycans that has been studied for its anti-albuminuric potential. Considering the effects of glycosaminoglycans on endothelial function and sodium homeostasis, we hypothesized that sulodexide may lower blood pressure (BP). In this meta-analysis, we therefore investigated the antihypertensive effects of sulodexide treatment.

METHODS

We selected randomized controlled trials that investigated sulodexide treatment of at least 4 weeks and measured BP at baseline and after treatment. Two reviewers independently extracted data on study design, risk of bias, population characteristics and outcome measures. In addition, we contacted authors and pharmaceutical companies to provide missing data.

RESULTS

Eight studies, totalling 3019 subjects (mean follow-up 4.4 months) were included. Mean age was 61 years and mean baseline BP was 135/75 mmHg. Compared with control treatment, sulodexide resulted in a significant systolic (2.2 mmHg [95% CI 0.3, 4.1], $P = 0.02$) and diastolic BP reduction (1.7 mmHg [95% CI 0.6, 2.9], $P = 0.004$). Hypertensive patients displayed the largest systolic BP and diastolic BP reductions (10.2/5.4 mmHg, $P < 0.001$). Higher baseline systolic and diastolic BP were significantly associated with larger systolic ($r^2=0.83$, $P < 0.001$) and diastolic BP ($r^2=0.41$, $P = 0.02$) reductions after sulodexide treatment. In addition, systolic ($r^2=0.41$, $P = 0.03$) and diastolic BP reductions ($r^2=0.60$, $P = 0.005$) were significantly associated with albuminuria reduction.

CONCLUSION

Our data suggest that sulodexide treatment results in a significant BP reduction, especially in hypertensive subjects. This indicates that endothelial glycosaminoglycans might be an independent therapy target in cardiovascular disease. Future studies should further address the BP lowering potential of sulodexide.

Introduction

Hypertension is the most important risk factor for cardiovascular and all-cause mortality worldwide and its prevalence is still increasing [1]. However, half of all hypertensive patients have an uncontrolled blood pressure (BP) and even in patients who have their BP controlled the residual cardiovascular risk remains high [2–5]. New therapeutic interventions may therefore help to control the cardiovascular burden of hypertension.

Sulodexide is a highly purified mixture of glycosaminoglycans (GAGs) that is currently marketed in a number of countries in Europe, South America and Asia for various cardiovascular conditions. GAGs are large, negatively charged, linear polymers that are present on the surface of all endothelial cells and in the extracellular matrix. Here, GAGs interact with a wide range of processes that are involved in the development of cardiovascular disease, including shear mediated nitric oxide (NO) production and non-osmotic sodium storage [6]. Sulodexide has been shown to improve endothelial function and lipid profiles, exert anti-inflammatory, anti-thrombotic and fibrinolytic activity, inhibit leucocyte adhesion and diminish platelet aggregation [7]. Because of these vasoprotective effects, sulodexide has been studied in numerous clinical trials. For instance, sulodexide has been shown to decrease claudication symptoms in peripheral artery disease patients and to prevent atherothrombotic events after acute myocardial infarction [8, 9]. In addition, a series of small studies demonstrated that sulodexide decreased albuminuria [10]. However, two recently performed large randomized controlled trials could not reproduce these findings [11, 12]. Noticeably, no clinical trials have thus far investigated the antihypertensive potency of sulodexide.

In this meta-analysis, we have therefore investigated whether sulodexide treatment results in a significant BP reduction when compared with control treatment in adult patients.

Methods

The primary objective of this systematic review and meta-analysis was to investigate the effect of sulodexide on BP in adult patients, after correction for control treatment.

Information sources and searches

In this meta-analysis, we adhered to PRISMA guidelines. MEDLINE, EMBASE and Cochrane library databases were searched (until October 2014) for clinical trials in which sulodexide was administered to adult subjects. The electronic search strategy was designed by two authors (ROE, NR) who were trained in systematic review searches (Supplementary Data). In addition, we used

bibliographies of previously published narrative reviews and editorials concerning sulodexide to search for eligible clinical trials. Articles were first evaluated based on title and abstract. Case reports, guidelines, editorials and reviews were excluded, as well as abstracts with a combination of title and abstract that indicated that the article could not meet the requirements of this review.

Study selection

For this review we considered randomized controlled trials in adult patients that investigated the effects of sulodexide on any medical condition. Studies were included when sulodexide treatment lasted at least 4 weeks and BP data were reported. We excluded studies with active treatment in the control arm. To ensure that the data set was as complete as possible we contacted corresponding authors and sulodexide manufacturers of studies that mentioned BP measurements, but not reported BP values. Two reviewers (ROE and NR) independently assessed the eligibility of each study. Disagreement was resolved through final discussion with a third reviewer (LV).

Data collection process and data items

We extracted data using a standardized data abstraction form. Data extraction was done by two independent reviewers (ROE and NR). We extracted data on BP changes in sulodexide and control groups. In addition, we collected data on key demographics such as age, gender, body mass index (BMI), baseline BP, plasma creatinine, diabetes prevalence, presence of albuminuria and use of renin-angiotensin system (RAS) inhibitors, and study characteristics such as study size, mean follow-up duration, publication year and inclusion criteria, and the incidence of adverse events. Adverse events were defined as serious adverse events or adverse events that led to study discontinuation of the patient.

Risk of bias in individual studies

In individual studies, two authors (ROE and NR) assessed the risk of bias according to the Cochrane Handbook Guidelines. The risk of bias was assessed for random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessment, incomplete outcome data and selective reporting.

Summary measures and synthesis of results

Quantitative analyses of outcomes were based on intention-to-treat analysis whenever possible. We calculated mean BP changes and 95% confidence intervals (CI) between baseline and after sulodexide treatment for each study to combine outcomes across trials. To correct for placebo effects and regression to the mean, we adjusted the mean BP difference for the observed BP change in parallel control groups (i.e. control-subtracted

effects). To investigate the effects of sulodexide both in normotensive and hypertensive subjects, we performed a stratified analysis for studies with baseline BP $\geq 140/90$ mmHg and $< 140/90$ mmHg.

We calculated the (anti-)albuminuric and proteinuric effects of sulodexide in percentage change from baseline (mean and standard deviation), corrected for control groups. To combine incidences of adverse events among trials, we calculated risk ratios for each study.

Statistical heterogeneity was identified by calculating I^2 that describes the percentage of total variation across studies that is due to heterogeneity [13]. We examined funnel plot asymmetry to explore the potential presence of publication bias. Data were analyzed using a random effects model.

Sensitivity and meta-regression analyses

The robustness of our results was tested by sensitivity analyses excluding open label trials and trials that did not keep track of antihypertensive treatment during follow-up. We used meta-regression analyses to test whether BP changes induced by sulodexide were associated with albuminuria reduction, a surrogate endpoint for both cardiovascular and renal outcome [14, 15], or patient characteristics such as age, gender, sulodexide dose, use of renin-angiotensin system inhibition and baseline BP. In these analyses, studies were weighted according to the inverse variance of the BP changes. Risk ratios for adverse events were log-transformed for linear regression analyses. Data were analyzed using Cochrane Review Manager Software (Review Manager 5.2) and SPSS (Version 21.0, SPSS, Inc., Chicago, IL, USA).

Results

Study selection

A total of 638 records were found after searching in MEDLINE, EMBASE and the Cochrane database and 93 full-text articles were reviewed (Figure 1). Eight studies containing thirteen comparisons, totalling 3019 participants, were included [10–12, 16–20].

Study characteristics

In seven studies, sulodexide treatment was compared with placebo while one study compared sulodexide with a control group that did not receive any treatment. Six out of eight studies investigated possible anti-albuminuric effects of sulodexide in diabetic patients. Three of these studies only included micro-albuminuric patients [11, 17, 20], one study only included macro-albuminuric patients [12] and two studies included both micro- and macro-albuminuric patients [10, 18]. In addition, one study investigated the effects of sulodexide on proteinuria from non-diabetic origin

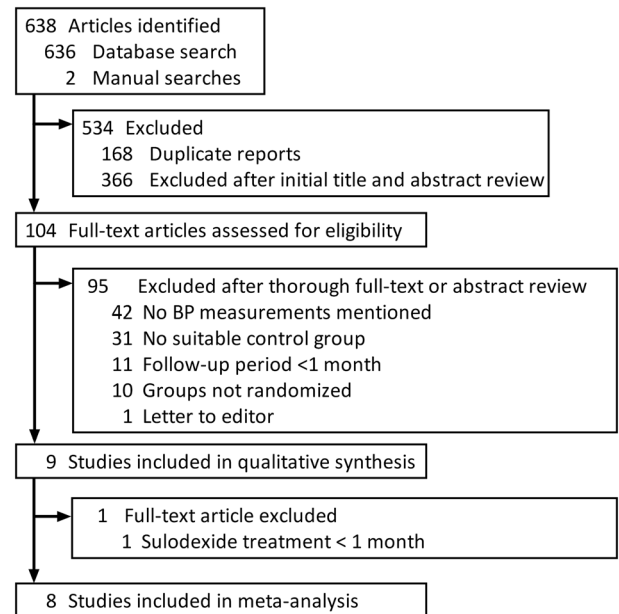


Figure 1

Selection process for studies included in the meta-analysis according to the PRISMA 2009 flow diagram

(IgA nephropathy) [16]. The remaining study investigated the effects of sulodexide on ulcer healing in patients with chronic venous insufficiency [19]. BP measurements were reported after 3 to 6 months of sulodexide therapy with an average treatment period of 4.4 months.

Patient characteristics

The mean age of participants was 61 (11) years, 73% were male and mean systolic BP (SBP) (135 (15) mmHg) and diastolic BP (DBP) (75 (10) mmHg) were within normal range (Table 1). The average BMI was 31.8 (11.5) kg m⁻² and mean serum creatinine was 141 (62) $\mu\text{mol l}^{-1}$. In six studies sulodexide was given on top of RAS inhibition [10–12, 16, 18, 20]. The mean administered sulodexide dose was 185 mg day⁻¹ and ranged from 50 to 400 mg among studies.

Risk of bias within and across studies

Seven out of eight studies were double-blinded. Three studies explicitly stated that no change in antihypertensive treatment was made during sulodexide or placebo treatment [10, 17, 18]. Four studies reported methods for BP measurements, all calculating mean values of three seated BP measurements after at least 5 min rest. Corresponding authors provided (additional) BP data for three studies. BP data for one study was retrieved after contact with the manufacturer (Alfa Wasserman, Bologna, Italy). Funnel plots were symmetrical by visual inspection suggesting that no publication bias was present.

Table 1

Characteristics of included studies

Study	Population	n	Treatment	FU (months)*	Age (years)	Male (%)	DM1/DM2 (%)	RASi (%)
Bang <i>et al.</i> [16]	Macroalbuminuric IgA nephropathy patients	28	SUL 150 mg	6	40 (13)	50	0/0	100
		25	SUL 75 mg		42 (13)	36	0/0	100
		24	Placebo		43 (12)	50	0/0	100
Coccheri <i>et al.</i> [19]	Chronic venous insufficiency patients	120	SUL 60 mg i.m. 20 days, 100 mg oral 70 days	3	63 (10)	44	NA/NA	NA
		110	Placebo		64 (10)	48	NA/NA	NA
Gambaro <i>et al.</i> [10]	Micro- and macro-albuminuric patients	55	SUL 200 mg	4	47 (13)	NA	56/44	58
		56	SUL 100 mg		47 (12)	NA	59/41	48
		56	SUL 50 mg		49 (12)	NA	54/46	48
		56	Placebo		47 (13)	NA	54/46	54
Heerspink <i>et al.</i> [20]	Microalbuminuric patients	52	SUL 400 mg	6	61 (11)	73	0/100	100
		50	SUL 200 mg		64 (9)	72	0/100	100
		47	Placebo		60 (12)	70	0/100	100
Lewis <i>et al.</i> [11]	Microalbuminuric patients	524	SUL 200 mg	6	62 (10)	75	0/100	100
		532	Placebo		62 (10)	77	0/100	100
Packham <i>et al.</i> [12]	Macroalbuminuric patients	619	SUL 200 mg	3	62 (9)	62	0/100	100
		629	Placebo		64 (10)	60	0/100	100
Solini <i>et al.</i> [18]	Hypertensive micro- and macroalbuminuric patients	12	SUL 100 mg	4	52 (10)	NA	0/100	17
		12	Placebo				0/100	
Velussi <i>et al.</i> [17]	Hypertensive microalbuminuric patients	24	SUL 100 mg	6	67 (14)	67	0/100	NA
		24	No treatment				0/100	

*when last BP measurements were performed in the entire cohort during sulodexide treatment. DM, diabetes mellitus; FU, follow-up; im intramuscular; RASi, renin-angiotensin system inhibition; SBP, systolic blood pressure; SUL, sulodexide; NA, not available.

Synthesis of results

Sulodexide treatment led to a significant control-subtracted BP reduction (Figure 2). SBP decreased by 2.2 mmHg ($P = 0.022$; $I^2=53\%$) while DBP decreased by 1.7 mmHg ($P = 0.004$; $I^2=59\%$). In two studies that included patients with an average uncontrolled BP at baseline (i.e. $>140/90$ mmHg) we observed a large SBP (10.2 mmHg, $P < 0.001$) and DBP reduction (5.4 mmHg, $P < 0.001$), while studies that included patients with a controlled BP at baseline showed a lesser SBP (1.0 mmHg, $P = 0.07$) and DBP reduction (1.0 mmHg, $P = 0.02$) (Figure 2). In the subgroups of patients with an average controlled or uncontrolled BP we found no heterogeneity for the outcomes of SBP and DBP reduction ($I^2 < 50\%$). Sensitivity analyses did not lead to a significant change in treatment effect.

Six comparisons demonstrated a reduction in albuminuria or proteinuria after sulodexide treatment while five comparisons, including two large recent trials, did not. The mean effect of sulodexide on albuminuria or proteinuria was a non-significant decrease of 6% (95% CI, -35% , 23% , $P = 0.70$). The change in albuminuria and proteinuria after sulodexide treatment was significantly associated with the degree of SBP ($r^2=0.41$, $P = 0.034$) and DBP reduction ($r^2=0.60$, $P = 0.005$) (Figure 3).

Seven out of eight trials reported the incidence of adverse events during sulodexide and placebo treatment.

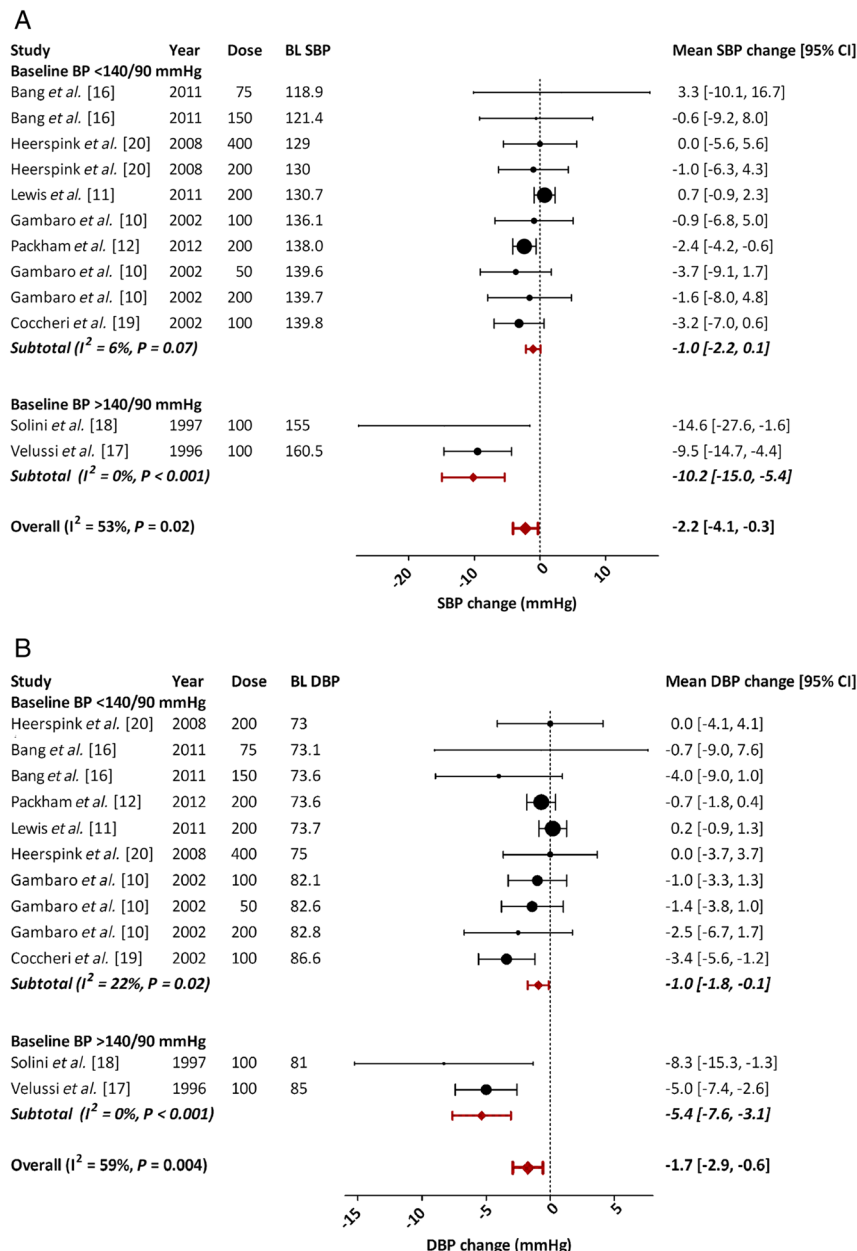
Comparable incidences of adverse events were found for sulodexide and placebo (risk ratio 1.07, 95% CI 0.93, 1.22, $P = 0.33$). Most adverse events that were reported were not believed to be related to the study medication.

Meta-regression analyses

We observed a significant positive association between baseline SBP and the observed drop in SBP ($r^2=0.83$, $P < 0.001$) as well as baseline DBP and the DBP reduction ($r^2=0.41$, $P = 0.024$) after sulodexide treatment. SBP reduction showed a significant positive association with total cholesterol concentrations ($r^2=0.65$, $P = 0.029$). In addition, higher total cholesterol concentrations and lower BMI were significantly associated with larger DBP reductions. These associations, however, did not remain significant after correction for baseline BP. Sulodexide dose, mean age, gender, length of follow-up, study size and serum creatinine were not associated with the effects of sulodexide on BP. The risk of adverse events was not associated with baseline BP, observed BP changes during treatment or sulodexide dose.

Discussion

The findings of this meta-analysis demonstrate that sulodexide has antihypertensive potency. Because

**Figure 2**

Studies have been separated according to mean baseline BP as hypertensive ($>140/90$ mmHg) or non-hypertensive ($<140/90$ mmHg). Studies were weighted by the inverse of variance assuming random effects. The diameter of the point estimate (circle), representing mean BP changes, is proportional to the weight of the study. BL, baseline; DBP, diastolic blood pressure; SBP, systolic blood pressure

included studies were randomized controlled trials of good methodological quality and we corrected for BP changes in parallel control groups, the observed BP lowering effects are neither caused by a placebo effect nor by regression to the mean. The significant SBP and DBP decrease in patients with uncontrolled hypertension equals BP reductions achieved after monotherapy with other classes of antihypertensive drugs [21]. In patients with controlled BP, sulodexide resulted in a minor, significant reduction in DBP, while SBP was not significantly

reduced. These effects were observed in subjects with high cardiovascular risk of which the majority was already being treated with antihypertensive drugs.

We could not observe a dose-dependent association between sulodexide dose and the degree of BP reduction. Because baseline BP was a strong covariate that had a large influence on the degree of BP reduction, this analysis cannot exclude possible dose-dependent effects of sulodexide. In three studies that investigated multiple sulodexide doses within one study, in patients with

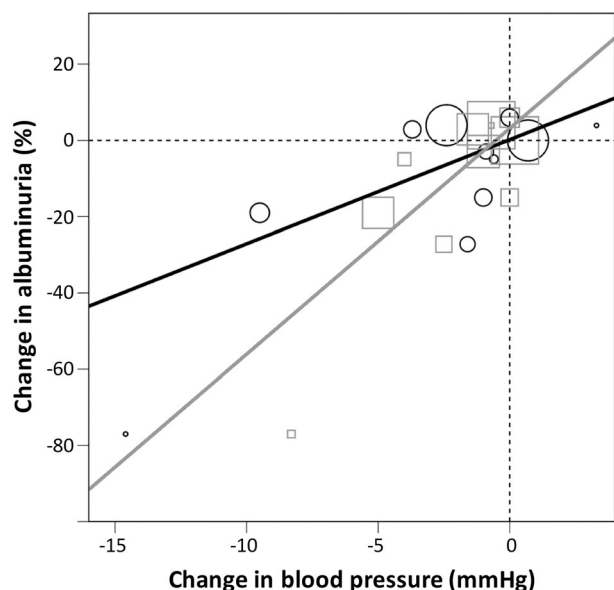


Figure 3

Linear regression analysis of the association between SBP (black) and DBP (grey) reduction and anti-albuminuric effects after sulodexide treatment. Changes in albuminuria were significantly associated with SBP ($r^2=0.41$, $P=0.034$) and DBP changes ($r^2=0.60$, $P=0.005$) induced by sulodexide

similar baseline BP, we could not observe a dose-dependent BP effect. Because patients in these studies had controlled BP, it cannot be excluded that the BP reduction in patients with uncontrolled BP may be larger. A higher incidence of adverse events may be anticipated for higher doses of sulodexide [22]. However, the rate of adverse events during sulodexide treatment was similar to placebo and higher doses were not associated with an increase in adverse events.

The BP lowering effects of sulodexide may relate to both increased NO production and non-osmotic sodium storage. Sulodexide has been demonstrated to increase NO availability in a rat model of chronic kidney disease [23]. This may be because of a reduction in inflammation or oxidative stress, both of which have been observed after sulodexide treatment and are known to decrease NO bioavailability [24–26]. An increase in endothelial surface layer (ESL) volume may be another mechanism by which sulodexide could increase NO production. The ESL is a dynamic layer on the luminal side of the endothelial cell that is home to a large amount of GAGs, especially heparan sulphate. Sulodexide is distributed to the ESL where it has been shown to restore reduced ESL dimensions present in diabetic patients [27–29]. As the ESL is an important mediator of shear-induced NO production, an increase in ESL volume following sulodexide treatment may lead to an increase in NO availability [30–32]. BP reductions by sulodexide therefore seem a logical result of endothelial function improvement that appears to be the common pathway of

many actions exerted by sulodexide [33–35]. Non-osmotic sodium storage may also contribute to the antihypertensive potency of sulodexide [6]. Sulodexide consists of negatively charged GAGs, which have been shown to be able to bind and osmotically inactivate sodium ions in the skin interstitium [36–38]. In addition, GAGs in the ESL have been shown to be able to bind sodium under flow conditions [39]. Considering the large systemic volume of the ESL, non-osmotic sodium storage in the ESL may have significant implications for BP and extracellular volume regulation [40]. Sulodexide may therefore increase the capacity for non-osmotic sodium storage and prevent sodium from deteriorating endothelial cell function or expanding extracellular volume and causing BP to rise [29].

By increasing NO availability and the non-osmotic ESL buffer capacity for sodium, sulodexide may be particularly beneficial in salt-sensitive hypertension and result in an additional BP reduction on top of other antihypertensive treatments. As salt-sensitivity is a major problem in resistant hypertension, sulodexide may contribute to the treatment of resistant hypertension [41]. This is supported by the results of our meta-analysis, in which most patients received sulodexide on top of antihypertensive treatment and showed an additional BP reduction. In addition, sulodexide has favourable characteristics that may reduce cardiovascular risk beyond BP. Sulodexide has been shown to diminish platelet aggregation and to exert anti-inflammatory, lipid lowering, anti-thrombotic and fibrinolytic actions [7]. It is therefore conceivable that sulodexide may be able to affect beneficially the residual risk of hypertensive patients that remains high despite maximum antihypertensive treatment [3]. Furthermore, as recently hypothesized by us and others, an increase in non-osmotic sodium storage capacity may help to control fluid overload in patients with heart failure and chronic kidney disease [6, 42]. A cardiovascular outcome trial in 3986 myocardial infarction patients demonstrated that sulodexide was able to reduce mortality and reinfarction rate compared with standard therapy, excluding antiplatelet and anticoagulant therapy [9]. Because a highly significant risk reduction of death from heart failure in the first months was not accompanied by a risk reduction of reinfarction rate, other mechanisms than the hypothesized anti-coagulant activity may have contributed to the cardiovascular benefit including BP lowering effects and an increase in non-osmotic sodium binding capacity.

In this meta-analysis, most included studies have investigated the ability of sulodexide to reduce albuminuria or proteinuria. Various underlying mechanisms have been suggested for the proposed anti-albuminuric/proteinuric effects of sulodexide, all of them assuming that sulodexide specifically targets the kidney. Our data show that greater reductions in albuminuria by sulodexide are associated with larger BP reductions. This

is consistent with previous studies that have demonstrated that lower BP is associated with less albuminuria, also in the lower BP ranges of the studies that were included in this meta-analysis [43]. This suggests that systemic effects of sulodexide should not be overlooked and may explain the contrasting finding of previous studies on albuminuria endpoints to a certain extent. Future studies investigating the kidney-specific effect of sulodexide should therefore correct for systemic BP reductions.

Limitations

We acknowledge some limitations in the interpretation of the data from this meta-analysis. First of all, methods of BP measurements were only provided in three trials and could be retrieved in one more after correspondence. Second, three studies did not keep track of anti-hypertensive medication use. This is most likely because these studies included patients with controlled BP. Although these limitations may induce bias, their influence is probably minor since seven out of eight studies were double-blinded and BP was not regarded as a primary outcome in any of the studies.

Conclusion

This meta-analysis provides evidence that sulodexide treatment results in a significant BP reduction, especially in hypertensive patients. Considering the anti-inflammatory and anti-thrombotic actions, it is conceivable that sulodexide may render additional cardioprotective benefits as compared with regular classes of antihypertensive agents. Future studies are needed to confirm the antihypertensive potency of sulodexide and investigate the mechanisms underlying the BP reducing effects. Finally, optimal dosing and combination strategies with current antihypertensive treatment for BP control deserve exploration.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work. DdZ was a member of the advisory board of Keryx Biopharmaceuticals in the previous 3 years. There are no other relationships or activities that could appear to have influenced the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Supplementary Data 1

Characteristics and the risk of bias table of included studies

Supplementary Data 2

Search strategy